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NOTE ON SOME EXPERIMENTS WITH ERGOTINE.

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It is needless to discuss the evidence of the clinical value of ergotine; its use as an ecbolic and as a hæmostatic is on most hands admitted. But the question in this, as in many other cases, is: How does the drug act? Do the contractions of the uterine fibres indicate a peripheral, *i.e.*, local, action; or do they represent a reflex act? Similarly—admitting that vascular spasm results from the action of ergot—is this spasm the result of direct action on the plain muscular fibres of the arterioles; or is it produced mediately through the nervous system?

As to the physiological data on the subject of the action of ergot Hermann (*Lehrbuch der Toxicologie*, 1874, pp. 384 *et seq.*) speaks very doubtfully. According to him, the action on the vessels is uncertain—*i.e.*, as to whether they do or do not contract. Similarly, as to the action on the heart, and the effect on blood-pressure, the results, according to Hermann, are both doubtful and contradictory. Wood, in his *Treatise on Therapeutics* (1881), discusses the subject at some length; and we must refer to this treatise for more detailed consideration of the question; suffice it here to say that the balance of evidence is in favour of the following two propositions:

1. Ergot causes spasm of the arterioles.
2. It produces very decided rise in blood-pressure.

As to the action on the heart, it appears that ergot, in full doses, causes unquestionably a fall in the frequency of the contractions. Eberty ascribes this to stimulation of the vagi; but on this point, as Hermann shows (*op. cit.*, p. 387), his statements are somewhat contradictory. Rossbach (quoted by Hermann) describes a curious ineo-ordinate action of the heart, in particular of the ventricle. At times, this latter showed peristaltic waves proceeding from base to apex. These experiments were made on the frog with Wenzell's ecbolin. This description by Rossbach recalls the action of digitalis on the heart; but it is certain that a systolic heart, if it occur, is a rare event after the administration of ergot; whilst, on the other hand, diastolic arrest has been in many cases recorded. It appears, further, that a primary fall in the blood-pressure is in many cases witnessed after the direct introduction of ergot into a vein. This primary fall is explained by Wood as a result of a weakening of the cardiac muscle from the direct action of the drug upon it. Thus, then, ergot would resemble the digitalis-group in its action on blood-pressure and on the arterioles; but it would contrast with the digitalis-group in its action on the heart. We must, however, not forget that digitalis, the most characteristic member of the group named after it, does occasionally arrest the heart in diastole. Boehm has explained this exceptional result as due to reflex inhibition, having found that, after section of the vagi, diastolic arrest was never witnessed in frogs (Wood, p. 137). It is clear that the same explanation may be advanced in the case of ergot; and this is the

explanation actually given by Eberty (Wood, p. 543), according to whom it is impossible to effect cardiac arrest by ergot after section of the vagi.

Leaving the question of the cardiac action of ergotine, let us return to a consideration of the action on the arterioles. In a recent series of experiments on the digitalis-group, the results of which have been given in a paper recently read before the Royal Medical and Chirurgical Society,[1] we endeavoured to establish for the members of this group a direct action on the arterial walls. Amongst others, we also made some experiments with ergotine, the results of which we will now shortly give.

The preparation used was ergotine (Bonjean's extract). Of this, we employed in our first experiment a 1 per cent. solution; in our subsequent ones, a 10 per cent.

Our method of experimentation was the same as that adopted for the members of the digitalis-group; it was as follows. The brain and spinal cord of a tortoise were destroyed, the shell of the animal then sawn transversely in half, and the soft parts divided. Into the abdominal aorta of the hinder half of the body a cannula was then tied. This cannula was fed by simple siphon-action, with saline solution, 0.6 per cent., made with tap-water. The course of the circulation was, accordingly, into the tissues through the abdominal aorta, and out by the cut veins. The escaping fluid drained from a glass plate into a suitable vessel and was accurately measured. The quantity of fluid which flowed through the vessels during each interval of five minutes was then recorded.

The head of pressure varied in the different experiments, but during each was maintained constant within about 0.5 centimètre, by constant additions to the supply-vessel, which was chosen of large capacity, so as to retard changes in level.

Experiment.—July 11. The temperature of room, 19.5° C. (67.1 Fahr.) Head of pressure, 31 centimètres.

	Outflow per 5 Minutes.		Outflow per 5 Minutes.
Saline solution[2] 0.6 per cent., supplied.	70 c.c.	8 c.c. ergotine in 100 c.c. saline.	63 c.c.
	66 „		61 „
	64 „		63 „
	64 „		60 „
0.5 c.c. ergotine (1 per cent. solution of Bonjean's extract) to each 100 c.c. of saline.	64 „		60 „
	60 „		56 „
	62 „		50 „
	60 „	Digitaline 1 c.c. (1 per cent. solution) in 100 c.c. saline.	46 „
	68 „		24 „
	64 „		8 „
2 c.c. ergotine in 100 c.c. saline.	60 „		3 „
	64 „		
	65 „		
	65 „		
	67 „		

In this experiment it may be observed that, till the strongest solution of poisoned saline (8 c.c. of ergotine solution in 100 c.c. saline) was employed, no diminution in the rate of flow was observed. Under this strongest solution a slight fall obtained, viz., from 67 c.c. to 50 c.c.

Our stock of ergotine being exhausted, we substituted a saline solution poisoned with digitaline (1 c.c. of 1 per cent. to 100 c.c. saline solution). The sudden fall in the rate of flow, from 50 c.c. to 3 c.c., contrasts well the powerful effect of digitaline in con-

[1] November 27th, 1883, "Investigations into the Action of the Digitalis-Group." See *Lancet*, December 1st, 1883.

[2] We may remark that the saline solution employed throughout was made with tap-water and not distilled water.

strieting the vessels, with the comparatively feeble action of ergotine in the strengths employed.

In our next experiment a mueh stronger solution of ergotine was used, viz., a 10 per eent. solution of Bonjean's extraet.

September 7th. Temperature of room, 15° C. (59° Fahr.) Hcad of pressure, 31.5 eentimètres.

	Rate of Flow per 5 Minutes.		Rate of Flow per 5 Minutes.
Saline solution only.	40 e.c. 30 „ 34 „ 35 „ 29 „	Ergotinc 4 c.c. (10 per eent. solution) in 100 e.c. saline.	39 c.c. 56 „ 50 „ 40 „ 40 „ 30 „ 24 „ 20 „ 16 „ 15 „ 13 „ 13 „

In this experiment, a very decided fall occurred during the circulation of the ergotised saline; but there are one or two points which require notiee: the first is, that the immediate effect of the ergotised solution was to eause a rise in the ratc of flow—from 29 e.c. to 56 c.e.—an increase of rate amounting to almost twice the rate at the moment of the addition of the ergot. The next point for notiee is, that the solution of ergotine (Bonjean's) was strongly aeid. Acid solutions have been shown by Dr. Gaskell (*Journal of Physiology*, vol. iii, No. 1, August 1880) to cause dilatation of the arterioles, and it is possible that the immediate inerease in rate may be thus explained. It may be mentioned that, early during the first interval of five minutes following the substitution of the ergotised solution for the simple saline, very energetie movements of the leg-museles oeeurred, but that these disappeared soon afterwards, and that thereupon the legs bceame quite flaeeid, and the pelvie museles did not respond by eontraetion to a tap or a pinch; it appeared as though the ergotised solution had killed them.

Our next experiment was made with a 10 per eent. solution of ergotine (Bonjean's extraet), whieh had been carefully neutralised with carbonate of soda.

September 10th. Temperature of room, 15.5° Cent. (59.9 Fahr.) Hcad of pressure, 31 centimètres.

	Rate of Flow per 5 minutes.		Rate of Flow per 5 Minutes.
Saline solution 0.6 per eent.	18 c.c. 18 „ 19 „ 24 „ 25 „	Ergotised solution replaced.	29 e.e. 19 „ 13 „ 13 „ 11 „
Ergotised saline (4 c.c. ergotine to 100 c.e. saline).	30 „ 34 „ 23 „ 23 „ 14 „ 13 „ 13 „	Saline solution replaced.	10 „ 15 „ 19 „ 22 „ 25 „
Saline solution replaced.	14 „ 18 „ 24 „ 25 „ 28 „	Ergotised solution replaced.	20 „ 13 „ 12 „

This experiment confirms very definitely thc previous two experi-

ments. We here note that, on three separate occasions, the rate of flow falls subsequently to the addition of ergotine, to again rise on resubstitution of the ergotised solution by unpoisoned saline. The fall in each case is very decided, viz.: in the first case, from 25 c.c. to 13 c.c.; in the second, from 28 c.c. to 11 c.c.; in the third, from 25 c.c. to 12 c.c. The movements of the hind limbs of the tortoise[3] became more active almost immediately after the first addition of the ergotine, then declined, and were speedily lost; but, in spite of this, the persistence of vitality of the arterioles is proved by the dilatation which in each case followed replacement of the ergotised solution by saline solution. In this experiment, acidity as a disturbing cause was eliminated, yet the first addition of ergotine was followed by a primary rise in the rate of flow; this rise, however, was but slight, and was much more transitory than was observed in the preceding experiment.

These experiments do not admit of much criticism; and, in concluding this brief contribution towards the pharmacology of ergot, we would restate in a few words the argument, the steps in which are:

1. The selection of the tortoise as an animal, the vitality of whose tissues is remarkably persistent, and therefore well adapted for lengthened experimentation;

2. The establishment of an artificial circulation through vessels removed from central nervous control;

3. The alternate addition to and subtraction from the circulation of the drug under experiment, viz., ergotine.

In how far we are justified in our conclusion that ergotine does act directly on the vessels, or, more strictly stated, does act independently of the central nervous system, we must leave to be decided by means of the experiments themselves.

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[3] These movements persist in the tortoise long after the spinal cord has been destroyed, as completely as this is possible by means of a wire.